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EXAMINER
SAKELARIS, SALLY A

ART UNIT	PAPER NUMBER
1634	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/869,554	Applicant(s) ORLEFORS ET AL.	
	Examiner Sally A Sakelaris	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1, 5, 7, and 8 recite the limitation "measuring the pyrophosphate released." There is insufficient antecedent basis for this limitation in claim 1. Neither the preamble, nor step (i), makes reference to a step including a pyrophosphate or the release thereof. The claim should be amended to clarify how and when the pyrophosphate to be measured came to be.

B. Claims 1, 5, 7, and 8 are also indefinite over the recitation of step (iii)'s " the nature of the nucleotide." The term "nature of the nucleotide" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. There is no fixed definition in the art for what constitutes the nature of the nucleotide. The preamble of the claim refers to the determination of the nucleotide base in a nucleic acid sample, but it is unclear if "the nature of the nucleotide" similarly refers to the base identity (i.e. A,T,G, or C) or instead to the presence or absence of a nucleotide, a mutation in the nucleotide, etc. The claim should be amended to clarify what exactly is meant by the "nature" of a nucleotide.

C. Claims 1, 5, 7, and 8 are further indefinite over the recitation of the "identification" of a nucleotide base that was previously "added." Neither the preamble, step (i), nor step (ii), make reference to a step including an addition of nucleotide bases. The claim should be amended to clarify how the identification of nucleotides that have never been added can occur or an addition step should be added to precede the identification step.

D. Claims 2, 6, 11, and 12 are indefinite over the recitation of "primer" in step (ii). It is unclear to what "primer" the claim is referring. Furthermore, the claim is indefinite over the recitation of "primer DNA" in step (iii), because it is not clear as to whether this is the same as or different from the "primer" in step (ii). The claim should be amended to clarify the purpose of this "primer."

E. Claims 2, 3, 4, 6, 9, 10, 13, 14, 15, and 16 are further indefinite over the recitation of "as required" in step (iv). The term "as required" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. There is no fixed definition in the art for what constitutes "as required". It is unclear by whom, or for what purpose the requirement is meant. The claim should be amended to clarify why the repetition of steps (ii) and (iii) would be a required step.

F. Claims 2, 6, 11, and 12 are even further indefinite over "extension of the primer" in step (ii) as it appears as applicants may have omitted a step of denaturation of their double stranded DNA in step (i). It is unclear therefore, how the extension of a primer could occur if the template on which it is being used, is still double stranded. The claim should be amended to clarify the intended action to be taken by this primer.

G. Claims 2, 6, 11, and 12 are indefinite. The claims are drawn to a method for identifying the sequence of a portion of DNA. However, the method recites a final step of detecting whether a nucleotide is added to a primer. The claims do not clarify how detecting whether a nucleotide has been added to a primer results in the identification of a sequence. Therefore, it is unclear as to whether the claims are intended to be limited to a method for identifying a sequence or a method for detecting whether a nucleotide has been added to a primer.

H. Claims 3, 9, 13, and 14 are indefinite as step (ii) refers to hybridizing DNA or primer to "predetermined areas." It is unclear how a hybridization step would occur between the nucleic acids of the DNA and primer and the surface of a microfluidic device. The claims should be amended to clarify exactly to what the DNA or primer would be hybridizing.

I. Claims 3, 9, 13, and 14 are further indefinite over the recitation of "measuring the release of pyrophosphate" as it is unclear how it is a consequence of the primer extension that the PPi is the entity being measured. It is unclear if the primer extension directly "released pyrophosphate" or if the PPi released in the DNA polymerase-catalyzed reaction is detected by the ATP sulfurylase- and luciferase-catalyzed reactions, and it is the resultant light that is actually being measured, not the PPi. The claim should be amended to clarify the chain reaction of events taking place as a consequence of the primer extension and the culminating entity that is actually being measured.

J. Claims 3, 9, 13, and 14 are indefinite. The claims are drawn to a method of "determining a nucleotide base." However, the method recites a final step of constructing a DNA sequence." The claims do not clarify how constructing a DNA sequence results in the

determination of "a nucleotide base." Therefore, it is unclear as to whether the claims are intended to be limited to a method for determining a nucleotide base or a method for constructing a DNA sequence.

K. Claims 4, 10, 15, and 16 are indefinite over the recitation of "attaching the sample DNA to a surface of the reaction chamber" as it is unclear how a nucleic acid can be attached directly to a surface of the microfluidic device. Applicant should amend the claim to clarify to what exactly the DNA sample is being attached and how this attachment functions.

L. Claims 4, 10, 15, and 16 are indefinite. Claim 4 needs to clarify the relationship between the extended primer and the "portion of sample DNA" so it is clear that when one determines the sequence of the extended primer, they have thereby determined the sequence of a portion of the sample DNA.

M. Claim 6 is indefinite over the recitation of "involves." The term does not clearly set forth how the detection step is performed. It is unclear as to whether a labeled terminator is added during the detection step or whether the claim is referring to the fact that the dideoxynucleotide (terminator) in step (i) of claim 1 is labeled to facilitate detection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1, 3, 5, 7, 9, and 13 are rejected under 35 U.S.C. 102(b) as being unpatentable over Ronaghi et al.(Anal. Biochemistry, 1996).

Interpreting claim 1's recitation of a "microfluidic device" to mean any device which is suitable to operate with liquids on a microliter scale, Ronaghi et al. teaches the methods of such a device. Ronaghi et al. teach a method of determining a nucleotide base in a nucleic acid sample comprising the steps of:

(i) Incubating the nucleic acid sample with about 5 pmol primer, DNA polymerase, and a deoxynucleotide triphosphate(Page 85(10)).

(ii) measuring the pyrophosphate released in step (i)(Page 85); and

(iii) identifying the nature of the nucleotide base added by measuring which nucleotide caused the release of pyrophosphate in step (ii), wherein this release is detected by light emitted from a luciferin luciferase reaction and is performed in real time(Page 85). Furthermore, as suggested by Ronaghi, his device "would provide a flow system, with small volumes, high speed and low cost"(Page 88), thus fitting one definition of "microfluidic device."

With respect to Claims 3, 9, and 13 Ronaghi et al. further teach a method of determining a nucleotide base in a nucleic acid sample comprising the steps of:

(i) attaching 0.8 pmol(Ronaghi, Fig. 5) of a single-stranded DNA by way of streptavidin-coated super paramagnetic beads on the surface of a solid support;

(ii) hybridizing small amounts of primer respectively to the same surface of a solid support;

(iii) adding the four different nucleotides to the immobilized template hybridized to a primer. The PPi released in the DNA polymerase-catalyzed reaction is detected by the ATP sulfurylase- and luciferase-catalyzed reactions in real time. The height of the signal is proportional to the number of bases which have been incorporated.

(iv) repeating step (iii) as required to construct a DNA sequence for the elongated primers, and hence for portions of the sample DNA(Fig.1, 85).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronaghi et al.(Anal. Biochemistry, 1996) in view of Mian et al.(US Patent 6,319,469 B1).

With respect to claims 1, 4, 5, 10 and 15 Ronaghi et al. teach a method of identifying the sequence of a portion of sample DNA by determining a nucleotide base pair in a nucleic acid sample comprising the steps of:

(i) Incubating the nucleic acid sample with about 0.8 pmol primer, DNA polymerase, and a deoxynucleotide triphosphate(Page 88, Fig. 5).

(ii) measuring the pyrophosphate released in step (i)(Page 85); and

(iii) identifying the nature of the nucleotide base added by measuring which nucleotide caused the release of pyrophosphate in step (ii), wherein this release is detected by light emitted from a luciferin luciferase reaction and is performed in real time(Page 85).

With respect to Claims 2 and 11, Ronaghi et al. teach a method for identifying the sequence of a portion of sample DNA comprising the steps of:

(i) immobilizing a double stranded DNA onto a solid support;

(ii) adding the four different nucleotides to the immobilized template hybridized to a primer. The PPi released in the DNA polymerase-catalyzed reaction is detected by the ATP sulfurylase- and luciferase-catalyzed reactions in real time. The height of the signal is proportional to the number of bases which have been incorporated.(Page 85)

With respect to Claims 3, 9, and 13 Ronaghi et al. further teach a method of determining a nucleotide base in a nucleic acid sample comprising the steps of:

(i) attaching 0.8 pmol(Ronaghi, Fig. 5) of a single-stranded DNA by way of streptavidin-coated super paramagnetic beads on the surface of a solid support;

(ii) hybridizing small amounts of primer respectively to the same surface of a solid support;

(iii) adding the four different nucleotides to the immobilized template hybridized to a primer. The PPi released in the DNA polymerase-catalyzed reaction is detected by the ATP sulfurylase- and luciferase-catalyzed reactions in real time. The height of the signal is proportional to the number of bases which have been incorporated.

(iv) repeating step (iii) as required to construct a DNA sequence for the elongated primers, and hence for portions of the sample DNA(Fig.1, 85).

With respect to Claims 1 and 8 (interpreting the "microfluidic device" as one of the preferred embodiments of the specification), Ronaghi et al. does not teach a method for identifying the sequence of a portion of sample DNA wherein the steps are performed in a microfluidic device that is a disk and the fluids are moved by centripetal force, such as that which is referred to on page 5, line 32 of the current specification. With respect to Claims 2 and 12 Ronaghi et al. does not teach forming immobilized double stranded DNA on one or more reaction areas in a microchannel structure of a microfluidic device that is a disk and the fluids are moved by centripetal force. With respect to Claims 3 and 14 Ronaghi et al. do not teach attaching DNA to a microfluidic device that is a disk and moving fluids by centripetal force. With respect to Claims 4 and 16, Ronaghi et al. does not teach adding sample DNA to a microfluidic device or moving the sample to a reaction chamber on the microfluidic device that is a disk and the fluids are moved by centripetal force

With respect to Claim 6, Ronaghi et al. does not teach a detection step that involves labeled terminator.

However, with respect to Claims 1 and 8, 3 and 13, 4 and 16, and 2 and 12 Mian et al. teach performing the previously taught methods of Ronaghi inside a microfluidic device. In consideration of claims 1, 3, 4, 8, 13, and 16 Mian et al. teach performing the steps of forming immobilized double stranded DNA on a reaction area in a microfluidic device, attaching or

hybridizing single stranded DNA, and plainly adding sample DNA to a predetermined area on a microfluidic device that is a disc and whose fluids can be moved to various chambers. Furthermore, the Mian reference adds teachings of a disc-shaped, microfluidic device that causes fluid movement through the use of centripetal force. The reference even further teaches that such methods and apparatus are advantageous as they fill the need in the art for a simple, flexible, reliable, rapid, and economical microanalytic and microsynthetic reaction platform for performing biological, biochemical, and chemical analyses and syntheses that can move nanoliter to microliter amounts of fluids. The reference provides that the invention also advantageously combines "wet" chemistry capabilities with information processing, storing and manipulating ability. The addition of the disc-shaped microfluidic device that exploits centripetal force, to this method for sequence identification, conferred the ability to properly mix reaction components, remove reaction side products, and isolate desired reaction products and intermediates.(Col 3, lines 5-25)(Col 48, line 67) Furthermore, with respect to claims 2 and 12, Mian et al. add the teaching of forming DNA to a "microchannel structure" within the microfluidic device. The reference teaches that; the unique disc shape and ability to move nanoliter to microliter amounts of fluid, including reagents and reactants, at rapid rates to effect the proper mixing of reaction components through the use of microchannel structures and centripetal force, provides a remedy for the many deficiencies of the status quo. The use of microchannels, functioning to separate micro-amounts of fluid reagents, and centripetal force, to move fluids into and out of reaction chambers, facilitates high-throughput analysis for both genome sequencing and routine clinical applications that require such multiplexability.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conducted the method of Ronaghi et al. in view of the methods of Mian et al. by incorporating a disc-shaped microfluidic device with microchannels and caused fluid flow through the use of centripetal force in order to have achieved the expected benefit of providing a method that could be used for the automation of larger sequencing projects and for the provision of a "high-throughput system."

With respect to Claim 6, Mian teaches a detection step that involves a labeled terminator (Col 49, lines 5-10). Mian et al. teach a method wherein the detection step comprises the DNA being transferred into a mixing chamber containing terminator solution by spinning the disk. Terminator solution typically comprises 100nl of a solution containing 5 picomoles of each deoxynucleotide and 0.5 picomoles of one dideoxynucleotide covalently linked to a fluorescent label. The set of dideoxynucleotide-terminated DNA fragments comprising the reaction mixture is then separated by capillary electrophoresis and the sequence of the fragments determined by laser-induced fluorescence detection. The reference further teaches that this mode of detection ie, discs comprising a multiplicity of these synthetic arrays with fluorescent labels, permits the simultaneous synthesis of a plurality of dideoxynucleotide-terminated oligonucleotides and therefore applicable in high throughput analysis of sequencing data or clinical approaches.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conducted the method of Ronaghi et al. in view of the methods of Mian et al. and to have added a labeled terminator, in order to have achieved the benefit of providing a method that, would permit the simultaneous synthesis of a plurality of

dideoxynucleotide-terminated oligonucleotides and therefore applicable in high throughput analysis of sequencing data or clinical approaches.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Friday from 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

10/01/02

Sally Sakelaris

CARLA J. MYERS
PRIMARY EXAMINER